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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/395,409	09/14/1999	CHARLES CANTOR	25491-2403D	6005

24961 7590 12/19/2003

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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/395,409	Cantor
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 14, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-55, 58-60, 63-76, 86, 88-125, 127, and 128* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-55, 58-60, 63-76, 86, 88-125, 127, and 128* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *1003*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 14, 2003 has been entered.

Specification

2. Applicant has amended claim 1. Claims 1-55, 58-60, 63-76, 88-125, 127, and 128 are currently pending in this application.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-27, 29-55, 58-60, 63-70, 73-76, 86, 88-125, and 127-128 are rejected under 35 U.S.C. 103 (a) over Koster (U.S. Patent 5,605,798) (February 25, 1997) in view of Cantor (U.S. Patent 5,503,980) (April 2, 1996).

Koster teaches a method for sequencing a target nucleic acid (Abstract), comprising the steps of:

a) providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid (Example 1 and Claim 1);

b) hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, wherein each probe comprises a single-stranded portion comprising a variable region (Example 1 and Claim 1 and Figure 1 and Column 4, lines 11-14 and Column 9, lines 28-43 and Figures 2-3); and

c) determining molecular weights for nucleic acids of the target array by mass spectrometry (Example 1 and Claim 1 and Figures 1-11);

whereby the sequence of the target nucleic acid is determined (Example 1 and Claim 1 and Figures 1-11).

Koster also teaches a method, wherein the molecular weights are determined by gel electrophoresis (Column 1, lines 61-66).

Koster also teaches a method, wherein the mass spectrometry comprises matrix-assisted laser desorption/ionization and electrospray (Examples 1-2).

Koster also teaches a method, wherein the mass spectrometry comprises time of flight analysis (Example 1 and Figures 9-10).

Koster also teaches a method, wherein two or more molecular weights are determined simultaneously (Example 2).

Koster teaches a method, further comprising the step of enzymatically extending the nucleic acid probes of the target array using the hybridized target nucleic acid as a template to form extended strands of DNA and RNA (Claims 9, 16, 20, and 43).

Koster teaches a method, wherein the step of extending is performed in the presence of chain elongating nucleotides and chain terminating nucleotides (Column 9, lines 54-67).

Koster teaches a method, wherein the array comprises nucleic acid probes having at least one mass-modifying functionality coupled to heterocyclic base, a sugar moiety or a phosphate group that does not interfere with hydrogen bonding for base-pair formation (Column 9, line 28 to Column 10, line 54 and Figure 6 and Claim 25).

Koster teaches a method, wherein the mass-modifying functionality is coupled to a purine and deazapurine at position N7 and to pyrimidine at position C5 or C6 (Column 9, line 8 to column 10, line 35).

Koster teaches a method, wherein the mass-modifying functionality is selected from F, Cl, Br, CF3, CH2F, and CHF2 and Si (C2H5)3 (Column 10, lines 16-35).

Koster teaches a method, wherein the mass-modifying functionality is -XR, wherein X is selected from -0-, SCN and R is selected from alkyls, alkoxys and aryls and polyethylene glycols (Column 10, lines 1-36).

Koster teaches a method, wherein the mass-modifying functionality is thiol moiety (Column 3, line 47 and column 8, lines 10-17).

Koster teaches a method, wherein the alkyl moiety is generated by using iodoacetamide (Column 9, lines 16-27).

Koster teaches a method, further comprising the step of removing alkali cations by ion exchange comprising ammonium carbonate (Column 9, lines 11-16 and column 13, lines 1-4).

Koster teaches a method, further comprising the step of ligating the hybridized target nucleic acid to the probes (Figure 5).

Koster teaches a method, wherein the target nucleic acid is provided from a biological sample of a patient or from a recombinant source (Column 7, lines 19-40 and Column 11, lines 19-55).t

Koster teaches a method, wherein the target nucleic acid and nucleic acid fragments and probes are between about 10 to about 1000 nucleotides in length (Examples 1-2).

Koster teaches a method, wherein each sequence of the nucleic acid fragments is homologous with at least a portion of the sequence of the target nucleic acid (Figures 1-8).

Koster teaches a method, wherein each sequence of the set of nucleic acid fragments is complementary with at least a portion of the sequence of the target nucleic acid (Example 1).

Koster teaches a method, wherein the fragments are provided by nuclease enzymatic digestion of the target nucleic acid (Column 4, lines 25-39).

Koster teaches a method, wherein the fragments are provided by physically cleaving the target nucleic acid (Examples 1-2).

Koster teaches a method, wherein the fragments are provided by enzymatic polymerization through polymerase chain reaction and the fragments comprise a nested set (Claims 9, 16, 20, and 43 and Examples 1-2).

Koster teaches a method, wherein the probes are single stranded (Examples 1-2 and Figures 1-6).

Koster inherently teaches a method, comprising the step of dephosphorylating the nucleic acid fragment by treatment with a phosphatase prior to hybridization (Column 8, lines 36-48).

Koster teaches a method, wherein the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination (Example 1 and Claim 1 and Figure 1 and Column 4, lines 11-14 and Column 9, lines 28-43 and Figures 2-3).

Koster teaches a method, wherein the variable region is about 4-20 nucleotides in length (Examples 1-2).

Koster teaches a method, wherein the array of nucleic acid probes are attached to a solid support selected from hybridization chips, beads, and combs (Figures 1-8 and Column 3, lines 60-67 and Examples 1-2 and Claim 30).

Koster teaches a method, wherein the probes are conjugated with biotin and the solid support is conjugated with streptavidin (Figure 4).

Koster teaches a method, wherein each probe is attached to the solid support by a photocleavable bond (Column 8, lines 18-60).

Koster teaches a method, wherein the cleavable bond is cleaved by an enzyme (Column 8, lines 36-48).

Koster teaches a method, wherein the chemical agent is reducing agent (Column 8, lines 36-40).

Koster teaches a method, wherein the electromagnetic radiation is visible radiation (Column 8, lines 18-34).

Koster teaches a method, comprising an oligonucleotide spacer between each probe and the solid support (Figures 1-8 and Column 7, line 65 to column 8, line 17).

Koster teaches a method, wherein the solid support comprises a matrix that facilitates volatization of nucleic acids for molecular weight determination (Column 2, lines 14-33).

Koster teaches an array of nucleic acid probes, comprising a collection of probes, wherein:

each probe comprises a single-stranded portion and a double-stranded portion (Figure 3);

each single-stranded portion comprises a variable sequence (Figure 3 and Examples 1-2);

the collection contains 4R probes, where R is the length of the variable region (Figures 1-3);

the collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination (Example 1 and Claim 1 and Figure 1 and Column 4, lines 11-14 and Column 9, lines 28-43 and Figures 2-3);

the array is attached to a solid support comprising a matrix that facilitates volatization of nucleic acids for molecular weight determination (Column 2, lines 14-33).

Koster teaches a system, comprising:

a mass spectrometer, a computer (Column 2, lines 33-45), and the array as described above.

Koster does not teach the method such that each member of the set hybridizes to a member of the array of probes and determining molecular weights of nucleic acids in the target array to identify hybridized probes.

Cantor teaches the method such that each member of the set hybridizes to a member of the array of probes and determining molecular weights of nucleic acids in the target array to identify hybridized probes (Abstract and Examples 2 and 4). Cantor also suggests that customized probes can be made, which necessarily indicates towards the construction of the probe arrays capable of hybridizing to each member of the target set (Column 10, lines 20-29).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method such that each member of the set hybridizes to a member of the array of probes and determining molecular weights of nucleic acids in the target array to identify hybridized probes of Cantor into the computerized method of sequencing of nucleic acids by mass spectrometry of Koster, since Cantor states, "This invention is directed to methods for sequencing nucleic acids by positional hybridization, to procedures combining these methods with more conventional sequencing techniques, to the creation of probes useful for nucleic acid sequencing by positional hybridization, to diagnostic aid useful for screening biological samples for nucleic acid variations, and to methods for using these diagnostic aids (Column 1, lines 10-16)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the method such that each member of the set hybridizes to a member of the array of probes and determining molecular weights of nucleic acids in the target array to identify hybridized probes of Cantor into the computerized method of sequencing of nucleic acids by mass spectrometry of Koster in order to improve the sequencing of nucleic acids. An ordinary practitioner would have been motivated to combine and substitute the method such that each member of the set hybridizes to a member of the array of probes and determining molecular weights of nucleic acids in the target array to identify hybridized probes of Cantor into the computerized method of sequencing of nucleic acids by mass spectrometry of Koster, in order to achieve the express advantages noted by Cantor, of an invention which provides methods for sequencing nucleic acids by positional hybridization, procedures combining these methods with

more conventional sequencing techniques, the creation of probes useful for nucleic acid sequencing by positional hybridization, diagnostic aid useful for screening biological samples for nucleic acid variations, and methods for using these diagnostic aids.

5. Claim 28 is rejected under 35 U.S.C. 103 (a) over Koster (U.S. Patent 5,605,798) (February 25, 1997) in view of Cantor (U.S. Patent 5,503,980) (April 2, 1996) further in view of Weiss (U.S. Patent 6,025,193) (February 15, 2000).

Koster in view of Cantor teach claims 1-27, 29-55, 58-60, 63-70, 73-76, 86, 88-125, and 127-128 as described above.

Koster in view of Cantor do not teach the generation of thiol moiety by using Beucage reagent.

Weiss teaches the generation of thiol moiety by using Beucage reagent (Column 19, lines 10-26).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the generation of thiol moiety by using Beucage reagent of Weiss into the computerized method of sequencing of nucleic acids by mass spectrometry of Koster in view of Cantor, since Weiss states, "By using the sulfurization reagent, each and every "O" group of the phosphodiester bond can be substituted with a sulfur group (Column 19, lines 19-21)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the generation of thiol moiety by using Beucage reagent of Weiss into the computerized method of sequencing of nucleic acids by mass spectrometry of Koster in view

of Cantor in order to improve the analysis of nucleic acids. An ordinary practitioner would have been motivated to combine and substitute the generation of thiol moiety by using Beucage reagent of Weiss into the computerized method of sequencing of nucleic acids by mass spectrometry of Koster in view of Cantor, in order to achieve the express advantages noted by Weiss, of a sulfurization reagent by which each and every "O" group of the phosphodiester bond can be substituted with a sulfur group.

6. Claims 71 and 72 are rejected under 35 U.S.C. 103 (a) over Koster (U.S. Patent 5,605,798) (February 25, 1997) in view of Cantor (U.S. Patent 5,503,980) (April 2, 1996) further in view of Sanghvi et al. (U.S. Patent 6,214,551) (April 10, 2001).

Koster in view of Cantor teach claims 1-27, 29-55, 58-60, 63-70, 73-76, 86, 88-125, and 127-128 as described above.

Koster in view of Cantor do not teach the selectively releasable bond is 4,4'-dimethoxytrityl or a derivative thereof including 3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid.

Sanghvi et al. teach the selectively releasable bond is 4,4'-dimethoxytrityl or a derivative thereof (Example 81, column 58, lines 3-32). Although Sanghvi et al do not teach the derivative 3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid in particular but Sanghvi et al disclose equivalent compounds and derivatives used for the same purpose (Example 81).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the selectively releasable bond 4,4'-

dimethoxytrityl or a derivative thereof and equivalent compounds and derivatives used for the same purpose of selectively releasing bonds of Sanghvi et al. into the computerized method of sequencing of nucleic acids by mass spectrometry of Koster in view of Cantor , since Sanghvi et al. state, "This invention is also directed to methods for the selective binding of RNA for research and diagnostic purposes. Such selective, strong binding is accomplished by interacting such RNA or DNA with compositions of the invention which are resistant to degradative nucleases and which hybridize more strongly and with greater fidelity than known oligonucleotides or oligonucleotide analogs (Column 31, lines 19-25)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the selectively releasable bond 4,4'-dimethoxytrityl or a derivative thereof and equivalent compounds and derivatives used for the same purpose of selectively releasing bonds of Sanghvi et al. into the computerized method of sequencing of nucleic acids by mass spectrometry of Koster in view of Cantor in order to improve the analysis of nucleic acids. An ordinary practitioner would have been motivated to combine and substitute the selectively releasable bond 4,4'-dimethoxytrityl or a derivative thereof and equivalent compounds and derivatives used for the same purpose of selectively releasing bonds of Sanghvi et al. into the computerized method of sequencing of nucleic acids by mass spectrometry of Koster in view of Cantor, in order to achieve the express advantages noted by Sanghvi et al., of an invention directed to methods for the selective binding of RNA for research and diagnostic purposes whereas such selective, strong binding is accomplished by interacting such RNA or DNA with compositions of the invention which are resistant to degradative nucleases and which hybridize

more strongly and with greater fidelity than known oligonucleotides or oligonucleotide analogs.

Response to Amendment

7. In response to amendment, 102(e) rejections and 103(a) rejections have been withdrawn. However, new 103(a) rejections have been included.

Response to Arguments

8. Applicant's arguments with respect to all pending claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. This phone number will be changed to (571)272-0740 on and from January 14, 2004. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this Group is (703) 746-4979. Any inquiry of a general nature or relating to the status of this application or

proceeding should be directed to the Group LIE Chantae Dessau whose telephone number is (703) 605-1237.

Arun Kr. Chakrabarti

ARUN K. CHAKRABARTI
PATENT EXAMINER

Arun Chakrabarti,

Patent Examiner,

November 21, 2003

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